Amendments to the Drawings

Attached are replacement sheets for the drawings. Applicants have amended FIG. 1 to delete label "75" (above 50), and have amended FIGS. 3, 4, and 6, respectively, to delete the labels "81, 85, and 87". No new matter has been added by way of these amendments.

Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

The development of scaffold materials for regenerating tissue *ex vivo* and for uses of such *ex vivo* regenerated tissue/scaffold combinations to treat patients *in vivo* has been a growing subject of interest in the prior art. Of relevance to the present invention are prior art uses of tissue scaffolds for *ex vivo* culture of oral tissues.

U.S. Patent No. 5,885,829 discloses use of tissue scaffolds made of a porous matrix for the *ex vivo* culturing and regeneration of oral tissues from isolated dental cells. Numerous polymers, both biodegradable and non-biodegradable, synthetic or natural scaffold materials were described as suitable for culturing oral tissues *ex vivo*. In particular, homopolymers of poly lactic acid (PLLA), poly [D,L-lactic acid] (PDLLA), poly-glycolic acid (PGA) and heteropolymers of lactic acid and glycolic acid, i.e., poly[lactic-co-glycolic acid] (PLGA), alone or in combination with polyvinyl alcohol (PVA), were shown to be effective for culturing fibroblasts isolated from dental pulp. Cells from dental pulp were first explanted, separated, and propagated in a monolayer culture using ordinary tissue culture techniques. In one exemplified method, the cultured cells were removed and then seeded onto a matrix of about 3 mm thickness made of a mat of PGA fibers. The seeded matrix was then incubated in growth medium and it was shown that the cultured fibroblasts were able to adhere to the PGA fibers and ultimately occupy the spaces between fibers. Tubular matrix scaffolds were made from porous PLLA, PDLLA, and PLGA two dimensional films using a particulate leaching technique. A three dimensional tubular matrix device was constructed by stacking the films on one another and chemically sealing the edges. The tubular matrix device was shown to allow growth of vascular tissue when implanted into the mesentery and omentum of rats. Of the combinations tested, PLLA and PDLLA were shown to maintain their structure *in vivo*, while PLGA based devices did not. PGLA devices were determined to have less resistance against compressional forces than PLLA or PDLLA. Other techniques for forming tubular matrices were also described, including bonding of PLLA, PGA, and PLGA tubes using a chloroform spray. In another example, a three dimensional "sponge matrix" was described for a tissue scaffold formed of PLA infiltrated with PVA or of PLGA at a ratio of 85:15 D,L lactic acid:glycolic acid. These sponge devices were shown to support

growth of seeded liver cells *ex vivo*. The devices were also implanted into the mesentery of rats with and without seeded cells and shown to support in growth of vascular tissue *in vivo*.

Human dental pulp cells were shown to propagate *ex vivo* better on a PGA matrix than on collagen or alginate based hydrogel matrices. Seeded cells grown in this manner *ex vivo* filled the spaces within the PGA matrix. This was eventually replaced by new tissue including tissue containing collagen which indicates the formation of an extracellular matrix. In another experiment, human gingival cells and pulp derived fibroblasts were shown to infiltrate a PGA matrix when seeded and cultured *ex vivo*, and to express human gene products when the seeded and cultured matrix was implanted subcutaneous in mice *in vivo*, even though the majority of cells in the implant were mouse fibroblasts. In addition it was disclosed that tissue scaffold materials could be used to deliver drugs by demonstrating that epidermal growth factor (EGF) could be entrapped in microspheres made of a 75:25 PLGA copolymer and slowly released into a buffer *in vitro* over 30 days. Further, hepatocyte cells seeded into cylindrical microspheres containing EGF and implanted into the mesentery of rats were shown to exhibit the biological effects of EGF on hepatocyte cellular activity over a 4 day period when implanted *in vivo*. Although this patent discloses a utility for using scaffold material for *ex vivo* propagation of oral tissues, it fails to disclose any therapeutic methods for the use of such *ex vivo* cultured cells for treating teeth *in vivo*, and fails to disclose the use of tissue scaffolds in the absence of *ex vivo* culturing.

U.S. Patent No. 6,281,256 discloses a process of preparing open pore matrices of a biodegradable polymer made of PLLA, PGA or PGLA polymers by using gas forming and particulate leaching steps to form pores in the matrices of the polymers. In a typical example of the disclosed process, a PLGA copolymer is formed in a mixture that includes a leachable particulate material. The mixture is molded, optionally under compression, to a desired size and shape and is subject to a high pressure gas atmosphere to dissolve gas in the copolymer. Then a thermodynamic instability is created by reduction of the pressure so that the dissolved gas nucleates and forms gas pores within the copolymer, causing expansion and fusion of the copolymer particles, creating continuous polymeric matrix still containing the particulate material. The particulate material is then leached from the polymeric matrix with a leaching agent creating a porous matrix. The amount and size of the particulate material used in the mixture determines the level of interconnectivity between open pores, the size of

the pores and the amount of pores in the final matrix (porosity). The interconnected matrices formed by this method have a porosity of between about 25% to 95-97% and exhibit high tensile strength with a tensile modulus of about 850 to 1100 kPa and a compression modulus of about 250 kPa or larger. Such matrices were disclosed as being useful for bone formation and guided tissue regeneration (GTR) where tissues could be grown within the matrix pores guided by the scaffolding material, which provides a surface for cellular attachment. The porous matrices could also be made to have a non-porous barrier one on end by forming an impermeable skin, or could be made of different levels of porosity throughout by altering the amount of leachable particulate material in different sections so that one section forms open pores and another does not. Such matrices were also shown to be capable of releasing a growth factor VEGF *in vitro*, over a period of 20 to 21 days. Use of such matrices was generally mentioned as having utility in regenerating oral tissues. The use of such matrices configured with an impermeable side was particularly suggested for treating periodontal disease by using the pores in one section of the matrix to grow periodontal ligament cells and providing a barrier in another surface of the matrix to prevent down growth of epithelial cells. However, no actual method was described for the use of such matrices *in vivo* without previously seeding the matrix and culturing the cells *ex-vivo*.

U.S. Provisional Patent Application Serial No. 60/166,191 describes methods for producing tissue scaffolds of PGLA using fused salt crystals of selected sizes to control the porosity, interconnectivity, and ease of manufacture of the scaffolds.

U.S. Patent No. 6,472,210 discloses a method of making a polymer scaffold having an interconnected passage-way of strutted pores with diameters in the range of about 0.5 to 3.5 mm. The polymer may be PLGA. The polymer is prepared by mixing a liquid polymer in a solution with an organic solvent such as DMSO, methylene chloride, ethyl acetated chloroform, acetone, benzene butanone, carbon tetrachloride, heptane, hexane or pentane. The liquid polymer solution is mixed with particles of 0.5 to about 3.5 mm in diameter. The particle/polymer mixture is then treated with a "non solvent" for the polymer, such as water, alcohol, dioxane or aniline, in a phase inversion step that precipitates the polymer/particle. The particle is then leached from the precipitate by treatment with a solvent that dissolves the particle material but not the polymer. The method and composition are said to be suitable for forming tissue scaffolds for use in regenerating tabecular bone, which has a high porosity and large strutted trabeculae widths on the order of about 0.14 mm

to about 0.3 mm. Such large macrospores would not be suitable for regenerating dentin or other oral tissues in the teeth.

WO 00/56375 and Murphy et al., *J. American Chemical Society* 124(9):1910-1917 (2002), disclose methods for patterning (mineralizing) tissue scaffold material formed into three dimensional wafers for bioimplants. In one aspect, the surface of tissue scaffolds such as, PGA, PLA and PLGA, are coated with minerals such as calcium chloride, and phosphate useful for orthopedic tissue mineralization. The scaffold material is treated by electromagnetic radiation or by an electron beam to cause surface degradation via photolysis or electrolysis. Lithographic techniques are disclosed for forming patterns on the surface to create the desired sites of degradation. Alternatively, chemical hydrolysis of the surface or direct soaking of the scaffold material in an appropriate mineral solution may be used to pattern the wafer. In any case, the modified surface of the scaffold contains functional groups, such as polar oxygen groups (carboxylates in particular) that promote calcium phosphate formation on the surfaces of the materials used to form the scaffold materials when the treated scaffold is immersed in an appropriate solution. Osteogenic cell precursors may be seeded onto the mineralized biomaterial *ex vivo*. Alternatively, bone cells were said to attach to the mineralized scaffold material *in vivo*. The growth factor VEGF was shown to be released from such mineralized tissue scaffold materials over time. While numerous utilities of this patterning technique are disclosed, there is no teaching of using the patterned tissue scaffolds for a therapeutic treatment of dental conditions *in vivo*.

Other publications describe use of tissue scaffold material or hydrogels to deliver morphogenic agents (or genes encoding the same) that promote growth or development of various tissues *in vivo* after *ex vivo* culture. Rutherford, R.B., *Euro. J. Oral Science* 109(6):422-444 (2001) discloses that *ex vivo* grown dermal fibroblasts transduced with an adenovirus expression vector expressing a cDNA encoding bone morphogenic protein 7 (BMP-7) were effective at inducing reparative dentinogenesis with apparent regeneration of the dentin-pulp complex when transplanted *in vivo* in ferrets having pulpitis. However, no effect was seen when a 10 fold range (2.5 μg to 25μg recombinant protein) was delivered directly to the pulp tissue. Rutherford R.B., et al; *Eur. J. of Oral Science* 108(3):202-206 (2000).

Sloan et al., *Archives of Oral Biology* 45(2):173-177 (2000) uses a hydrogel of agarose beads soaked in BMP-7 to deliver the protein to tooth slices cultured *ex vivo* in a

semi solid agar and disclosed a localized increase in extracellular matrix secretion by odontoblasts at the site of application. Nakashima, M., *Archives of Oral Biology* 12:1085-89 (1994) demonstrated that recombinant BMP-2 and BMP-4 induced dentin formation in amputated pulp of dogs *in vivo* when condensed on a powdered carrier comprised of dried type 1 collagen and proteoglycans. In a prior publication, BMP-2 and BMP-4 were shown to induce dentin formation in amputated pulp when condensed on the same the same type of delivery material. Nakashima, M., *J. Dental Research* 73(9):1515-1522 (1994).

Other types of materials such as various modified hydrogels also provide tissue scaffold-like functions for propagating various tissue. Anderson et al, *Proc. Nat'l Acad Sci USA* 99(19):12025-30 (2002), disclosed that an alginate based hydrogel modified with the tripeptide sequence RGD promoted cell multiplication and bone tissue-like growth plates when chondrocytes were transplanted *ex vivo*.

U.S. Patent No. 6,413,498 discloses a mixture of cationic and anionic ion exchange resins charged with Ca^{2+}, F^- and PO_4^{3-} in molar ratio of 2:1:1 for use in a filler for the treatment of caries. These resins, typically made of polystyrene, promote remineralization of dentin to form tissue having a composition and hardness close to that of original dentin. Such resins, which are disclosed to also be useful as components of dentifrice products, are not suitable as a tissue scaffold to promote regeneration of the cell types that are required for healthy dentin. Moreover, such resins are believed to leave organic residue upon contact with teeth.

U.S. Patent Publication No. 2002/0119180 A1 and Young et al., *J. Dent. Res.* 81(10):695-700 (2002) each describe regenerating multiple dental tissues in organized tooth structures *in situ* by *ex vivo* seeding of enamel and pulp organ tissues on a PGA/PLLA or PLGA scaffold formed in the shape of a human teeth. The *ex vivo* cultured tissue/scaffold combinations were collagen coated and then implanted in the omentum of rats where they were cultured *in situ*. The *in situ* cultured tissue were shown to develop mineralized structures indicative of enamel surrounding dentin, and to develop into odontogenic cell types, including, ameloblasts, odontoblast-like cells, putative cemetoblasts and cementum. While the experiment demonstrated the potential feasibility of regenerating whole teeth by *ex vivo* seeding and *in vivo* culturing of isolated dental tissue, there is no disclosure of any method of treating dental tissue *in vivo*.

While the prior art recognizes the utility of using tissue scaffolds for growing tissue *in vitro* or for treating bone lesions *in vivo*, there remains a need in the art for methods and devices for treating dental conditions *in vivo* using such tissue scaffold. The present invention provides for such methods and devices.

The objection to claims 73-76 is respectfully traversed in view of the above amendments.

The rejection of claims 31, 43-45, 60, 61, and 77-81 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed in view of the above amendments.

The rejection of claims 1, 9-16, and 27-33 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,885,829 to Mooney et al. ("Mooney") is respectfully traversed.

Mooney discloses the generation of oral tissue from viable cells using *ex vivo* culturing on a structural matrix. The regenerated oral tissue or matrix-tissue structure may then be implanted in the body to form a new functional oral tissue. However, Mooney does not insert a tissue scaffold into a hole in a tooth and regenerate dentin *in vivo*, as claimed. To highlight this distinction, claims 1 and 29 have been amended to require that the tissue scaffold inserted into the hole does not include *ex vivo* cultured tissue. Support for this amendment is found in the present application at page 6, lines 1-5 and lines 20-21.

Since Mooney clearly fails to teach the claimed invention, the rejection based on this reference is improper and should be withdrawn.

The rejection of claims 72 and 75-81 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,822,278 to Oliva et al. ("Oliva") is respectfully traversed.

Oliva shows a dental instrument for use in facilitated placement and fixation of dental veneers for bonding on a patient's teeth. This device includes a light weight handle for coupling to a source of vacuum via tubing 22. Probe 30 projects from the handle with suction cup 40 being attached to the proximal end of the probe, valve assembly 32 closes and opens fluid access of the probe to vacuum source 26. However, Oliva does not teach a device with an attachment at the distal end of the vacuum tube to permit fluid communication between a vacuum source and the vacuum tube nor a valve assembly positioned at a distal end of the vacuum tube proximate to the claimed vacuum source. Since Oliva does not teach the claimed invention, the rejection under 35 USC § 102 based on this reference is improper and should be withdrawn.

The rejection of claim 4 under 35 U.S.C. § 103(a) for obviousness over Mooney is respectfully traversed for substantially the same reasons noted *supra*.

The rejection of claims 5 and 6 under 35 U.S.C. § 103(a) for obviousness over Mooney in view of U.S. Patent Application Publication No. 2004/0058442 to Shi et al. ("Shi") is respectfully traversed.

Shi teaches the use of dental stem cells to regenerate dentin/pulp tissue. However, Shi does not implant the stem cells without *ex vivo* culturing and thus does not overcome the above-noted deficiencies of Mooney.

The rejection of claims 7, 8, 24-26, 34, and 41-49 under 35 U.S.C. § 103(a) for obviousness over Mooney in view U.S. Patent No. 5,871,360 to Kato et al. ("Kato") is respectfully traversed.

Kato is cited for disclosing a dental filling material comprising fluoride and calcium phosphate. Since Kato does not, however, overcome the above-noted deficiencies of Mooney, this rejection cannot be maintained.

The rejection of claim 73 under 35 U.S.C. § 103(a) for obviousness over Oliva in view of U.S. Patent No. 2,885,782 to Groves et al. ("Groves") is respectfully traversed.

Groves shows a vacuum device assembly controlled by a manual dial 80. Groves does not, however, overcome the above-noted deficiencies of Oliva. Therefore, this rejection is improper and must be withdrawn.

The rejection of claim 74 under 35 U.S.C. § 103(a) for obviousness over Oliva in view of U.S. Patent No. 5,855,562 to Moore et al. ("Moore") is respectfully traversed.

Moore shows a dental vacuum system having an in-line filter 22. Moore does not, however, overcome the above-noted deficiencies of Oliva. Therefore, the rejection based on the combination of Oliva and Moore is improper and should be withdrawn.

The drawings are objected to under 37 CFR § 1.84(p)(5) for various informalities. To overcome this objection, minor amendments to the drawings have been made and replacement sheets are attached.

The specification is objected to for various informalities. To overcome this objection, minor amendments to the specification have been made.

In view of all of the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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